Antiarrhythmic drugs, patients, and the pharmaceutical industry: value for patients, physicians, pharmacists or shareholders?

A.A.M. Wilde, P. Langendijk

Antiarrhythmic drugs no longer seem to be big business. After the unexpected CAST trial results (excess mortality in the class 1C antiarrhythmic drug treatment arms in patients with coronary artery disease (CAD) and abundant ventricular extrasystoles),[1] antiarrhythmic drug treatment became less popular for CAD patients. Since this category of patients represents the majority of cardiology patients with chronic disease, these results impacted on the antiarrhythmic drug market. In the years that followed, the use of class 1C drugs was even further discouraged. Sotalol was also shown to hurt CAD patients (the SWORD trial) and even amiodarone was shown to have only a minimal benefit – if any – for this category of patients.[2] Only a few new drugs survived the experimental development phase and the initial clinical trials (e.g., azimilide).[3]

The above results and associated decreased use of antiarrhythmic drugs led pharmaceutical companies to withdraw class I drugs from the market, with the exception of the class IC drugs that remain in use, in particular for the treatment of atrial fibrillation. As a consequence, both class 1A and 1B drugs gradually disappeared. The list is quite long and without doubt non-profitability is the main reason. In chronological order the following drugs have disappeared from the market: Ajmaline i.v. (1996, Solvay), Mexiletine capsules (2001, Boehringer-Ingelheim), Procainamide durettes (2001, BMS), Tocainide tablets (2003, AstraZeneca) and Disopyramide extended-release tablets (2003, AstraZeneca). For some of these drugs, there are alternative routes to obtain them, but these are insecure and more costly. For example, mexiletine can still be (and actually is) imported from Germany by the 'Internationale Apotheek' in Venlo, among others. As a final climax to this story (so far), AstraZeneca informed physicians in November 2005 that their quinidine durettes would no longer be marketed (as of 1 January 2006). This left the cardiologist with direct-release quinidine sulfas 200 mg (also advised by AstraZeneca in their discontinuation announcement), the same drug but with a dosage regimen of at least four times daily. It is a shame that AstraZeneca refers doctors to this alternative, which is impracticable and by no means easy for our patients.

Our personal experience relates to a relatively stable young male ARVC (arrhythmogenic right ventricular cardiomyopathy) patient on quinidine durettes, who completely deteriorated within a few weeks on the alternative quinidine sulfas, simply because an adequate dose regimen (4 times daily) is not compatible with a reasonable life and compliance expectancy, in particular not in young individuals.

In a recent simple hand-raised questionnaire (September 2006) at a meeting of the Netherlands Heart Rhythm Association, it appeared that all electrophysiogists in tertiary referral centres treated some of their patients with quinidine durettes. Most of the time, the choice of drug is (was) a last resort in the treatment of malignant ventricular arrhythmias and is surprisingly often effective. Given the antiarrhythmic drug effect, the most relevant side effect (i.e. proarrhythmia) is taken for granted. This is a reasonable and balanced choice because all too often the patients are already implanted with an internal defibrillator (ICD). By subsequently taking the drug off the market, these practitioners are confronted with significant problems as all the available alternative drugs have already been tried.

The patient described in this issue of the Netherlands Heart Journal is a good example.[4] Diagnosed as symptomatic Brugada syndrome in 2004, he received an ICD. After successful defibrillation in 2005, he presented with an arrhythmic storm in 2006, which was successfully treated with isoproterenol and quinidine. The latter drug was continued and isoproterenol could

A.A.M. Wilde
Department of Cardiology, Amsterdam Medical Centre, Amsterdam, the Netherlands
P. Langendijk
Hospital pharmacist, Amsterdam Medical Centre, Amsterdam, the Netherlands

Correspondence to: A.A.M. Wilde
Department of Cardiology, Amsterdam Medical Centre,
PO Box 22660, 1100 DD Amsterdam, the Netherlands
E-mail: a.a.wilde@amc.uva.nl

be discontinued within a few days. Indeed, chronic quinidine has been shown to be effective in the long term,[5] and this patient does not have many alternatives to the chronic use of quinidine. At present and, in this case, thanks to AstraZeneca's policy, direct-release quinidine sulfas is the only choice in the long term. Brugada syndrome patients are predisposed to having nocturnal arrhythmias.[6] It is clearly to be expected that with direct-release quinidine sulfas, serum concentrations will be lowest during that time of night when the most protection is needed (unless the patient wakes up at night to take his medication). Disopyramide, the other alternative advised by AstraZeneca, is actually contraindicated (i.e., proarrhythmic) in this setting.

The yearly costs of drug registration in the Netherlands are only a mere € 980 and are not dependent on the drug revenues. Nevertheless, it is clear that the antiarrhythmic drugs discussed here are not profitable. In the Netherlands, only an estimated few dozen patients will be on chronic use. From an economic point of view, it is therefore understandable that pharmaceutical companies like AstraZeneca discontinue the production and distribution of these drugs. On the other hand, these companies have to realise that this places rare patients at immediate risk of death and confronts their cardiologists with major problems. Pharmaceutical companies also need to be aware that they do have more obligations to society than serving 'shareholder value'. In this case, the immediate action in favour of more return on investments of blockbusters and fewer costs on the side of less profitable drugs, such as the antiarrhythmic quinidine, might bounce back as a boomerang when society decides to boycott products of companies that refuse to take their social responsibility. Big Pharma has a lot to learn from the second most profitable industry after Pharma: the oil industry. Shell (Brent Spar) and Exxon (Exxon Valdez) have learned their lesson in this respect the hard way with a lot of collateral damage and image destruction.

AstraZeneca is one of the only drug companies still developing new antiarrhythmic drugs. On the other hand, it is unacceptable that only blockbusters, including me-too preparations such as Atacand and Crestor, are aggressively marketed, leading to satisfied shareholders, while at the same time, they no longer produce critically useful drugs for rare patients (with relatively low production and registration costs). In this regard, responsible action would have been to sell their durette to a generic company, so that the product remained available on the Dutch market. Their slogan 'life inspiring ideas' is simply not valid for the patients who are in need of drugs like quinidine. The shareholder comes first, second to the patient's (quality of) life. The quinidine story is a clear example of this policy.

Very recently we were also informed that procainamide i.v. ampulles (pronestyl) will also be discontinued as of March 2007, the only reason again being commercial/economic. Apparently, Bristol Myers Squibb does not consider it of interest to inform the cardiologists who use this drug on a regular basis in the treatment of malignant ventricular arrhythmias of this decision. As stated above, pharmaceutical companies have a clear preference for their shareholders, who come first. The mission statement of BSM: 'Bristol Myers Squibb is a pharmaceutical and related health care products company whose mission is to extend and enhance human life' does not apparently refer to patients with life-threatening arrhythmias. ■

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